REMARKS

Claims 41 and 44 having been amended, the pending claims in the above-identified patent application are claims 34-51.

Reconsideration and withdrawal of the rejections are respectfully requested. No new matter has been added.

Information Disclosure Statement

The Examiner has requested a copy of the references cited in the 1449 mailed by Applicants on March 8, 2002. A copy of the aforementioned references is provided herewith.

Rejections Under 35 U.S.C. §101

The Examiner rejected claim 40 under 35 U.S.C. §101 as being directed towards non-statutory subject matter. Specifically, the Examiner states that the terms "cultured cell" read on the natural, non-patentable, state of the cultured cell. This rejection is respectfully traversed.

Claim 40 is directed towards a cultured cell into which has been introduced an expression which includes the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide wherein the encoded polypeptide comprises amino acid residues 31-346 of SEQ ID NO:2; and a transcription terminator, wherein the cell expresses the polypeptide encoded by the DNA segment. Applicants would like to draw the Examiner's attention to page 15, lines 23-26 of the instant application, which discloses that "further analysis of the genomic DNA revealed a polynucleotide encoding a full length secreted zsig46 polypeptide, wherein the polynucleotide was characterized by two introns." One of skill in the art would clearly appreciate that the cultured cells of claim 40, which contains an expression vector having cDNA (i.e., no introns) encoding a zsig46 polypeptide, are directed towards patentable subject matter not occurring in nature.

Accordingly, reconsideration and withdrawal of the rejection to claim 40 under 35 U.S.C. §101 are respectfully requested.

The Examiner rejected claims 34-51 under 35 U.S.C. §101 as allegedly not being supported by either a specific and substantial credible utility or a well established one. This rejection is respectfully traversed.

Applicants respectfully submit that the rejection is contrary to both the law and the United States Patent Office's own examination guidelines. The application of these standards to biotechnology inventions is discussed in the January 5, 2001 Federal Register Notice of the United States Patent Office's Utility Examination Guidelines. Section II.B.1(c)(1) and (2) of the January 5, 2001 "Utility Examination Guidelines" states "[a]n invention has a well-established utility if a person of ordinary skill would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties...), and the utility is specific, substantial, and credible" (66 FR 4, p. 1098). Moreover, "[a] patent examiner must accept a utility asserted by an applicant unless the Examiner has sound scientific reasoning to rebut the assertion" (66 FR 4, p. 1096). To establish a *prima facie* showing of lack of utility, "the Office must ... provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing ... the PTO must do more than merely question operability - it must set forth factual reasons which would lead one of skill in the art to question the objective truth of the statement of operability" (MPEP 2107.02(IV)).

Applicants would like to draw the Examiner's attention to page 25, lines 24-30, of the specification which discloses that "the zsig46 polypeptide-encoding gene is located in close proximity to the endothelin-B receptor gene, which is one of the 13-linked susceptibility gene for Hirschsprung disease. Hirschsprung disease is a multigenic disorder that involves a defect in the development of neural crest-derived cell lineages." Upon reading the specification, one of skill in the art would immediately appreciate that zsig46 has a specific, substantial, and credible utility.

The Examiner has provided no evidence or scientific basis to refute the assertions of utility for the polypeptides of the present invention. The invention indeed has a specific asserted and a well-established utility for the claimed polypeptides that are supported by the specification. Thus, Applicants submit that the Examiner has not established a *prima facie* showing of lack of utility, because it has not provided sound scientific reasoning to rebut the assertion of utility in the application and the evidence

presented by Applicants therein. In view of the Examiner's apparent failure to note and evaluate this evidence, Applicants submit that a *prima facie* showing of no specific and substantial credible utility has not been made.

For the above reasons, Applicants respectfully submit that the invention recited in claims 34-51 is useful. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §101 are respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 34-51 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated on page 7 of the Office Action that "it is apparent that the claimed clone is essential to the claimed invention and the deposit is necessary for an adequate written description and enablement for the claimed invention." This rejection is respectfully traversed.

Applicants wish to point out that the enablement requirement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 USPQ 214, 219 (CCPA 1976). A considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Jackson, 217 USPQ 804 (Bd. App. 1982).

Applicants respectfully submit that ATCC-deposited plasmid pZp9 is NOT required for a skilled artisan to use the present invention as claimed. On the contrary, plasmid pZp9 is merely an example of an expression vector that can be used to facilitate production of zsig46. Furthermore, the instant application discloses numerous vectors and cells to assist a skilled artisan to produce a zsig46 polypeptide. Thus, Applicants submit after reading the specification of the instant application one of skill in the art would be able to make and use zsig46 without undue experimentation.

The Examiner also indicated on page 7 of the Office Action that Applicants should amend the specification to provide the current address to the American

Type Culture Collection (ATCC). Applicants are confused by this request. The application discloses the ATCC address at the time of filing. Applicants respectfully request the Examiner to provide a basis for such a request.

Because a reasonable basis to question the enablement provided for the claimed invention was not provided in the Office Action, the burden of proof under 35 U.S.C. §112, first paragraph has not been satisfied, and a *prima facie* case of lack of enablement has not been made. "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling supports." MPEP §2164.04. Reasons for uncertainty of the enablement are required even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments.

Applicants respectfully submit that one of skill in the relevant art would be able to make and use the invention as claimed, as the skilled artisan would be able to readily identify an isolated polypeptide and utilize such by consulting the present specification. Here the Examiner has offered no reason to doubt the truth of the statements in the specification.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-51 under 35 U.S.C. §112, first paragraph, are respectfully requested.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 35, 37, 39, 41, 44 and 51 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. These rejections are respectfully traversed.

Claim 35 was rejected as lacking antecedent basis and for enlarging the scope of independent claim 34 with the phrase "residues 1-346 of SEQ ID NO:2". Applicants do not understand this rejection. One way a claim may lack clarity is by

lacking antecedent basis. This, however, is not the case. The above phrase was not included in independent claim 34 as it is a narrowing limitation introduced into dependent claim 35. With respect to "residues 1-346 of SEQ ID NO:2" enlarging the scope of independent claim 34 ("residues 31-346 of SEQ ID NO:2'), Applicants would like to respectfully point out that a longer sequence typically narrows the scope of a claim, not enlarge. Accordingly, reconsideration and withdrawal of the rejection to claim 35 under 35 U.S.C. §112, second paragraph, are respectfully requested.

Claim 37 was rejected for lacking clarity. Specifically, the Examiner stated on page 8 of the Office Action that "it is not clear how the DNA encodes affinity tag linkage". This rejection is respectfully traverse. The term "affinity tag" is defined on page 8, lines 7-25 to denote "a peptide segment that can be attached to a polypeptide to provide for purification of the polypeptide or provide sites for attachment of the polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), substance P, Flag™ peptide (Hopp et al., Biotechnology 6:1204-1210, 1988; available from Eastman Kodak Co., New Haven, CT), streptavidin binding peptide, or other antigenic epitope or binding domain. See, in general Ford et al., Protein Expression and Purification 2: 95-107, 1991. DNAs encoding affinity tags are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ)." Thus, one of skill in the art would clearly understand that "affinity tag" of the present invention encompasses both tags that can be encoded with a zsig46 polypeptide (e.g., fusion protein) and tags that are conjugated to zsig46 post-translationally. Accordingly, reconsideration and withdrawal of the rejection to claim 37 under 35 U.S.C. §112, second paragraph, are respectfully requested.

Claim 39 was rejected for a lack of clarity. Specifically, the phrase "residues 1-28 or 1-30 of SEQ ID NO:2" allegedly lacked an antecedent basis. This rejection is respectfully traversed. The above phrase was not included in independent claim 34 as it is a narrowing limitation introduced into dependent claim 39. Accordingly,

reconsideration and withdrawal of the rejection to claim 39 under 35 U.S.C. §112, second paragraph, are respectfully requested.

Claims 41 and 44 were rejected for a lack of clarity. Specifically, the terms "E. coli" allegedly lacked clarity". Per the Examiner's suggestion, claims 41 and 44 have been amended to recite "Escherichia coli," thereby rendering the Examiner's rejection moot. Accordingly, reconsideration and withdrawal of the rejection to claims 41 and 44 under 35 U.S.C. §112, second paragraph, are respectfully requested.

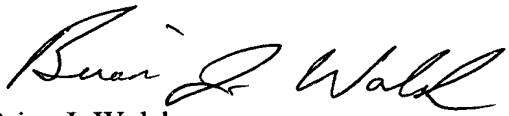
Claim 51 was rejected for lacking clarity for the use of the term "another". This rejection respectfully traversed. Applicants would like to draw the Examiner's attention to page 23, lines 16-19, which discloses that "the other polypeptide may be a signal peptide to facilitate secretion of the fusion protein, a therapeutically active protein, a targeting protein or the like". Thus, one of skill in the art would clearly understand "another" polypeptide fuses to a zsig46 polypeptide comprising amino acid residues 31-346 of SEQ ID NO:2. Accordingly, reconsideration and withdrawal of the rejection to claim 51 under 35 U.S.C. §112, second paragraph, are respectfully requested.

Claim 51 was also rejected for lacking clarity for the use of the term "portion." Specifically, the Examiner stated on page 8 of the Office Action that "it is not clear how a fusion protein comprises a 'portion'". Applicants do not understand this rejection. Claim 51 is directed towards a fusion protein which includes a first portion (polypeptide comprising amino acid residues 31-346 of SEQ ID NO:2) and a second portion (another polypeptide). The first portion and second portion are encoded in frame ("fused") by the isolated polynucleotide to produce a fusion protein. Thus, one of skill in the art would clearly understand the term "portion" as recited in claim 51. Accordingly, reconsideration and withdrawal of the rejection to claim 51 under 35 U.S.C. §112, second paragraph, are respectfully requested.

Summary

It is respectfully submitted that claims 34-51 are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' Agent at (206) 402-6540, if it is believed that prosecution of this application may be assisted thereby.

Respectfully Submitted,



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Enclosures:

Petition and Fee for Extension of Time (in duplicate)
Amendment Fee Transmittal (in duplicate)
IDS & PTO-1449
87 References
Postcard